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Pharmacokinetics and Exposure Response Relationships of Ustekinumab in Patients With Crohn's Disease

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BACKGROUND & AIMS: Ustekinumab is a monoclonal antibody that binds with high affinity to the p40 subunit of human interleukin 12 (IL12 and IL23) that has been approved for treatment of patients with moderate to severe Crohn's disease (CD). However, there are few data on its pharmacokinetic properties or the relationship between drug exposure levels and patient response. We collected data from 2 Phase 3 induction studies and 1 maintenance study to determine ustekinumab's pharmacokinetic features, relationship between exposure and response, and optimal serum concentrations for efficacy. **METHODS:** We collected data on serum concentrations of ustekinumab and efficacy from induction studies of patients with moderate to severe CD given ustekinumab for 8 weeks following a single intravenous dose (either 130 mg or approximately 6 mg/kg). We collected the same data from a maintenance study of patients with a response to ustekinumab in the induction study who then received subcutaneous injections (90 mg) every 8 or 12 weeks for 44 weeks. At week 44 of the maintenance study (52 weeks after treatment began), patients were evaluated for the primary endpoint of clinical remission (defined as a CD activity index score below 150 points), endoscopic markers of efficacy, and serum level of C-reactive protein. Ustekinumab concentration data were categorized into quartiles and relationships between exposure and response were assessed. Optimal concentration cutoff values were evaluated using receiver operating characteristic curve analysis. **RESULTS:** Serum concentrations of ustekinumab over time were proportional to dose and did not differ significantly between the induction studies. In the maintenance study, ustekinumab concentration reached the steady state by the second maintenance dose; the median trough concentration was approximately threefold higher in patients given ustekinumab at 8-week intervals compared with 12-week intervals. Ustekinumab serum concentrations associated with rates of clinical remission and endoscopic efficacy endpoints, correlated inversely with level of C-reactive protein, and did not associate with use of immunomodulators. Trough concentrations of ustekinumab of 0.8 (or even up to 1.4 μg/mL) or greater were associated with maintenance of clinical remission in a higher proportion of patients than patients with lower trough concentrations. **CONCLUSIONS:** In an analysis of data from Phase 3 studies of patients with moderate to severe CD, we found serum concentrations of ustekinumab to be proportional to dose and associate with treatment efficacy. Concentrations of ustekinumab did not seem to be affected by cotreatment with immunomodulators. Clinicaltrials.gov no. NCT01369329 (UNITI 1), NCT01369342 (UNITI 2), and NCT01369355 (IM-UNITI).

Keywords: UNITI Trials; Inflammatory Bowel Disease Treatment; IBD; Anti-IL12/23.

Crohn's disease (CD) is a chronic idiopathic inflammatory bowel disease (IBD) that can affect any portion of the intestinal tract[1–3] and is histologically characterized by granulomas, fissuring ulceration, submucosal fibrosis, and transmural gut infiltration of lymphocytes and macrophages.[4,5] Biologic agents have transformed the treatment of CD, with tumor necrosis factor (TNF) antagonists at the forefront,[6–11] most often used in patients who do not respond or are intolerant to treatment with corticosteroids and/or oral immunosuppressants.[12,13] However, a large proportion of patients with CD either do not respond to treatment with TNF antagonists or have only a transient response that later requires dose escalation or switching to another therapy.[6,10,14–18] Thus, there is a significant medical need for novel, safe, and effective therapies for moderately to severely active CD, particularly in patients who do not respond, lose response, or are intolerant to treatment with TNF antagonists.

In nonclinical studies, the proinflammatory cytokines interleukin 12 (IL12) and interleukin 23 (IL23) have been implicated in the pathophysiology of CD with multiple lines of evidence suggesting that CD is mediated by T_h1 and/or

Abbreviations used in this paper: 6-MP, 6-mercaptopurine; AUC, area under the curve; AZA, azathioprine; CD, Crohn's disease; CDAI, Crohn's Disease Activity Index; CRP, Creactive protein; ECLIA, electrochemiluminescent immunoassay; ER, exposureresponse; IBD, inflammatory bowel disease; IL12, interleukin 12; IL23, interleukin 23; IV, intravenous; MSD, Meso Scale Discovery; MTX, methotrexate; PK, pharmacokinetic(s); q8w, every 8 weeks; q12w, every 12 weeks; ROC, receiver operating characteristic; SC, subcutaneous; SES-CD, Simple Endoscopic Score for Crohn's Disease; TNF, tumor necrosis factor.

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EDITOR'S NOTES

BACKGROUND AND CONTEXT

Ustekinumab is approved for the treatment of patients with Crohn's disease (CD); however, data on its pharmacokinetic (PK) properties and the relationship between its systemic exposure and efficacy in this patient population is sparse.

NEW FINDINGS

The researchers characterized the PK of ustekinumab in CD, established a positive association between ustekinumab concentration and efficacy, and identified optimal concentration targets during induction and maintenance.

LIMITATIONS

This study focused on the influence of drug levels but did not quantify the potential impact of other patient or disease related factors on the efficacy of ustekinumab in CD.

IMPACT

This research provides important guidance in the treatment of CD with ustekinumab, highlighting data useful in further research on the application of therapeutic drug monitoring and the PK basis for employing ustekinumab monotherapy.

T_h17 cells.[19–26] Ustekinumab, a fully human immunoglobulin G1 kappa monoclonal antibody that binds with high affinity to the p40 subunit of human IL12 and IL23, has recently been approved for the treatment of moderately to severely active CD in adults. Ustekinumab prevents IL12 and IL23 bioactivity by preventing their interaction with their cell surface receptor protein IL12Rβ1. Through this mechanism of action, ustekinumab effectively neutralizes IL12 (T_h1)- and IL23 (T_h17)-mediated cellular responses. Evidence for the efficacy of ustekinumab in CD was first supported by the results of a proof of concept Phase 2a study of ustekinumab in patients who had moderate to severe CD[27] and then in the CERTIFI Phase 2b study of ustekinumab in patients with CD who did not respond or were intolerant to TNF antagonist therapy.[28] These Phase 2 studies formed the basis for the Phase 3 program of ustekinumab treatment for patients with CD, which consisted of 2 induction studies (UNITI-1 and UNITI-2) that led into a single randomized-withdrawal maintenance study (IM-UNITI), results for which have been previously reported.[29] The UNITI-1 trial included patients who met the criteria for primary or secondary nonresponse to TNF antagonists or had unacceptable side effects, whereas the UNITI-2 trial included patients in whom conventional therapy failed or unacceptable side effects occurred.

There is currently a lack of ustekinumab pharmacokinetics (PK) and exposure-response (ER) data in CD from large, randomized controlled trials. These data are critical to therapeutic drug monitoring, which is an important area of focus for gastroenterologists treating IBD. Here, we report on ustekinumab PK and ER relationships using data derived from these previously reported Phase 3 induction and maintenance studies in CD (3 randomized, placebo-controlled, double-blind trials), which comprised the largest cohort to date of ustekinumab-treated patients with CD.[29] Understanding the PK and association of ustekinumab exposure to efficacy outcomes and identification of optimal concentration thresholds may ultimately further the ability to individualize treatment of patients with CD.

Materials and Methods

Patients and Study Design

Detailed design and clinical results of the UNITI-1, UNITI-2, and IM-UNITI trials have been reported.[29] Briefly, all 3 trials were Phase 3, randomized, double-blind, placebo-controlled, parallel-group, multicenter studies. UNITI-1 and UNITI-2 were 8-week induction studies in patients with moderately to severely active CD. Clinical responders to ustekinumab at week 8 of induction treatment from UNITI-1 and UNITI-2 comprised the primary analysis population in IM-UNITI, a 44-week randomized-withdrawal maintenance study. The institutional review board or ethics committee at each study site approved the protocols, and all patients provided written informed consent. All authors had access to the study data and have reviewed and approved the final manuscript.

The UNITI-1 trial studied patients with moderate to severe CD (CD Activity Index [CDAI] score of 220 to 450) who previously did not respond, lost response, or were intolerant to TNF antagonists (n = 741). These patients were randomized to receive a single intravenous (IV) induction dose of placebo, a fixed ustekinumab dose of 130 mg, or a tiered dose of ustekinumab approximating 6 mg/kg (260 mg [weight $\leq$55 kg], 390 mg [weight >55 kg and $\leq$85 kg], or 520 mg [weight >85 kg]), referred to hereafter as ~6 mg/kg. Of the 741 randomized patients, 740 were included in the PK/ER analyses.

In the UNITI-2 trial, patients with CDAI scores of 220 to 450 who had not responded to or were intolerant to conventional therapy (corticosteroids or immunomodulators) but not TNF antagonists (n = 628) were randomized to receive the same dosage regimens as the UNITI-1 trial. Of the 628 randomized patients, 68% were naïve to prior TNF antagonists, and 626 of the 628 were included in the PK/ER analyses.

In UNITI-1 and UNITI-2, all patients were evaluated at week 6 (induction) for the primary endpoint of clinical response, defined as a reduction from baseline in the CDAI score of $\geq$100 points, although patients with a baseline CDAI score of $\geq$220 to $\leq$248 were considered to be in clinical response if a CDAI score of <150 was attained. The first major secondary endpoint of clinical remission at week 8 was defined as a CDAI score of <150 points.

In the IM-UNITI trial, patients in the primary efficacy population were responders to ustekinumab induction in either UNITI-1 or UNITI-2 (n = 397) and were randomized 1:1:1 at week 0 of that study to receive subcutaneous (SC) placebo or 1 of 2 ustekinumab maintenance regimens (ustekinumab 90 mg SC every 12 weeks [q12w] through week 36 [ie, at weeks 0, 12, 24, and 36] or ustekinumab 90 mg SC every 8 weeks [q8w] through week 40 [ie, at weeks 0, 8, 16, 24, 32, and 40]). Of the 397 randomized patients, 387 were included in the PK/ER analysis. At week 44 of IM-UNITI, 52 weeks after induction week 0, patients were evaluated for the primary endpoint of clinical remission, defined as a CDAI score of <150 points. ER

was also assessed at week 24, as it was the only concurrent trough time point for both the q8w and q12w ustekinumab regimens. A patient disposition diagram is shown in Supplementary Figure 1 and a study design schematic is shown in Supplementary Figure 2.

Study Evaluations and Analyses

Serum ustekinumab concentrations (hereafter referred to as ustekinumab concentration[s]) were measured in blood samples collected at scheduled visits through week 8 of UNITI-1 and UNITI-2 and through week 44 of IM-UNITI (Supplementary Table 1) using a validated electrochemiluminescent immunoassay (ECLIA) method on the Meso Scale Discovery (MSD) platform (Gaithersburg, MD). The lowest quantifiable concentration in a sample for the ECLIA method using the MSD platform was 0.1688 μg/mL (data on file). Because steady state was invariably attained by week 24 of the maintenance study for both ustekinumab maintenance regimens, average trough concentrations through week 44 were obtained by computing the arithmetic mean of patients observed trough concentrations (q12w: weeks 24 and 36; q8w: weeks 24, 32, and 40). The relationship between clinical remission and trough ustekinumab concentration quartiles in maintenance also were examined at week 24 of IM-UNITI, the timepoint where q8w and q12w shared a preadministration trough.

To assess disease activity, CDAI scores were used to determine clinical response and clinical remission, as defined previously. Additionally, endoscopic endpoints were assessed at week 44 (maintenance) using the Simple Endoscopic Score for Crohn's Disease (SES-CD)[30] in the subset of patients participating in the endoscopy substudy. Briefly, the scoring of the video endoscopies for the SES-CD was performed by a single reader at a central facility who was blinded to treatment group. Patients with a baseline SES-CD score $\geq$3 (indicating mucosal ulceration in at least 1 segment) were included in the endoscopy analyses.

The association between ustekinumab concentration and serum C-reactive protein (CRP) was also evaluated. CRP was measured with a validated high-sensitivity CRP immunonephelometry assay using the Siemens BNII Nephelometer (Covance Central Laboratory Services, North Yorkshire, UK) with a lower limit of quantification of 0.2 mg/L.

Antibodies to ustekinumab were assessed at baseline and week 6 of the induction study, and at weeks 0, 12, 24, 36, and 44 of the maintenance study. These analyses were performed using a validated and drug-tolerant ECLIA on the MSD platform, in which ustekinumab was used to capture and detect induced immune responses to ustekinumab. The assay also can detect anti-ustekinumab antibodies in the presence of up to 100 μg/mL of ustekinumab. Patients were classified as positive if antibodies were detected at any time in their serum sample.

Statistical Analysis

All ustekinumab concentration data were summarized for each treatment group using descriptive statistics that were calculated at each sampling timepoint. Missing ustekinumab concentration data were not imputed, and the data handling rules for the efficacy variables were previously described.[29] The relationships between ustekinumab concentration and clinical remission and CRP concentration were assessed. A 1-sided Cochrane-Armitage trend test was used to evaluate the presence of a trend in the proportion of patients with a clinical efficacy outcome across ustekinumab concentration quartiles. For comparisons of variables across concentration quartiles, a nonparametric 1-way analysis of variance based on the median score was used for continuous and ordinal variables, whereas a Fisher exact test was used for categorical variables. Optimal cutpoints of ustekinumab concentration associated with efficacy outcomes were determined using receiver operating characteristic (ROC) curve analysis. All statistical testing was performed at the .05 significance level.

Results

Baseline Patient Characteristics

Among the 1366 UNITI-1 and UNITI-2 patients included in the PK/ER analyses (Supplementary Figure 1), baseline demographic and other characteristics were representative of an adult population with moderately to severely active CD and were balanced between the treatment groups (Supplementary Table 2; Table 1).

Pharmacokinetics

All induction dose groups had peak median ustekinumab concentrations at week 0 (induction), 1 hour after IV infusion. Ustekinumab concentrations were proportional to dose and similar between UNITI-1 and UNITI-2 (Figure 1).

In the UNITI-1 trial median peak ustekinumab concentrations 1-hour post infusion at week 0 (induction) were 43.6 μg/mL and 129.1 μg/mL for the 130 mg and $\sim$6 mg/kg dose groups, respectively. At week 8, median ustekinumab concentrations were 2.1 μg/mL and 6.4 μg/mL for the 130 mg and $\sim$6 mg/kg dose groups, respectively.

In UNITI-2, median peak ustekinumab concentrations 1-hour post infusion at week 0 (induction) were 39.8 μg/mL and 124.4 μg/mL for the 130 mg and $\sim$6 mg/kg dose groups, respectively. At week 8, median ustekinumab concentrations were 2.0 μg/mL and 6.3 μg/mL for the 130 mg and $\sim$6 mg/kg dose groups, respectively.

Among IV ustekinumab responders randomized to placebo maintenance, median ustekinumab concentrations were undetectable by week 12 in recipients of 130 mg and by week 16 in those who had received the $\sim$6 mg/kg induction dose (Figure 2). In contrast, median ustekinumab concentrations were maintained above detectable limits through week 44 of IM-UNITI among patients randomized to either ustekinumab maintenance regimen (Figure 2). Ustekinumab concentrations reached steady state by the second SC maintenance dose (ie, 16 weeks after induction [week 8 of IM-UNITI] for q8w and 20 weeks after induction [week 12 of IM-UNITI] for q12w). Median preadministration ustekinumab concentrations were consistent through week 44 for both 90 mg q8w (ranging from 2.0 μg/mL to 2.2 μg/mL at IM-UNITI weeks 8, 16, 24, 32, and 40) and 90 mg q12w (ranging from 0.6 μg/mL to 0.8 μg/mL at IM-UNITI Weeks 12, 24, and 36) (Figure 2). Thus, median trough concentrations in the ustekinumab 90 mg q8w group were approximately threefold greater than in the 90 mg q12w group.

Table 1. Comparison of Baseline Patient Characteristics by Serum Ustekinumab Concentration Quartiles at Week 8 of Induction and at Week 24 of Maintenance Among Patients Treated with Ustekinumab in the UNITI-1, UNITI-2, and IM-UNITI Studies

Characteristic					
Baseline values at induction week 0 Median values					
Ustekinumab concentration at week 8 (induction)					
	All	Q1	Q2	Q3	Q4	P^a
N	701	175	175	176	175	
Age, *y*	36.0	32.0	36.0	37.0	41.0	.004
Body weight, *kg*	68.5	66.4	66.8	69.9	72.3	.064
CDAI[b]	302.0	324.0	305.0	294.5	292.0	.017
Disease duration from time of diagnosis, *y*	8.4	6.9	9.1	7.8	10.2	.135
Fecal calprotectin, *μg/kg*	473.4	727.8	473.4	374.3	242.3	<.001
Fecal lactoferrin, *μg/mL*	88.2	202.4	102.6	61.6	39.3	<.001
Albumin, *g/dL*	3.6	3.2	3.6	3.7	3.8	<.001
CRP, *mg/L*	8.4	22.5	9.2	5.6	5.3	<.001
Proportions						
Male gender, %	43.1	48.6	44.6	38.6	40.6	.245
Antibody-to-ustekinumab status (positive), %	3.1	5.7	0.6	2.9	3.4	.042
History of TNF antagonist use, %	64.9	69.1	65.1	65.3	60.0	.359
Concomitant immunomodulator use at baseline (Y), %	33.4	33.1	33.7	34.1	32.6	.993
Corticosteroid use at baseline (Y), %	36.0	38.3	34.9	39.2	31.4	.411
Ustekinumab concentration at week 24 (maintenance)						
	All	Q1	Q2	Q3	Q4	P^a
N	191	47	48	48	48	
Age, *y*	35.0	39.0	31.0	35.0	37.5	.050
Body weight, *kg*	67.6	70.5	67.3	64.3	70.9	.318
CDAI[b]	299.0	307.0	310.5	292.5	300.0	.377
Disease duration from time of diagnosis, *y*	7.0	6.7	8.1	7.0	7.7	.876
Fecal calprotectin, *μg/kg*	523.3	595.9	550.0	523.5	318.1	.026
Fecal lactoferrin, *μg/mL*	104.6	172.5	128.4	107.8	36.9	.058
Albumin, *g/dL*	3.6	3.4	3.6	3.8	3.9	<.001
CRP, *mg/L*	8.0	19.4	10.2	6.9	2.6	<.001
Proportions						
Male gender, %	44.0	55.3	41.7	33.3	45.8	.187
Antibody-to-ustekinumab status (positive), %	2.6	6.4	2.1	0.0	2.1	.227
History of TNF antagonist use, %	53.9	59.6	45.8	60.4	50.0	.398
Concomitant Immunomodulator use at baseline (Y), %	39.3	46.8	35.4	41.7	33.3	.532
Corticosteroid use at baseline (Y), %	34.0	31.9	31.3	41.7	31.3	.658

ANOVA, analysis of variance; N, number of patients; Q, quartile; Y, yes.
[a]For comparisons of variables across ustekinumab concentration quartiles, a nonparametric 1-way ANOVA based on the median score was used for continuous and ordinal variables, whereas a Fisher exact test was used for categorical variables.
[b]CDAI scores range from approximately 0 to 600, with higher scores indicating worse disease and a 50-point change indicating the minimal clinically important difference.

Serum ustekinumab concentrations were similar between patients who were on azathioprine (AZA), 6-mercaptopurine (6-MP), or methotrexate (MTX), compared with those who were not on these drugs (Supplementary Figure 3).

Exposure Response: Ustekinumab Concentrations and Efficacy Outcomes

To assess the relationship between efficacy and systemic exposure to ustekinumab, concentrations of ustekinumab at induction week 8 and maintenance week 24, as well as average trough concentrations through week 44 were categorized into quartile groups. The proportions of patients in clinical remission (CDAI score <150 points) were summarized by these quartiles.

In both induction trials, combining the 130 mg and ~6 mg/kg dose groups, higher remission rates were observed in the 2 higher ustekinumab concentration quartiles at week 8, compared with the 2 lower quartiles (Figure 3*A* and *B*), although this pattern was more apparent in UNITI-2. This

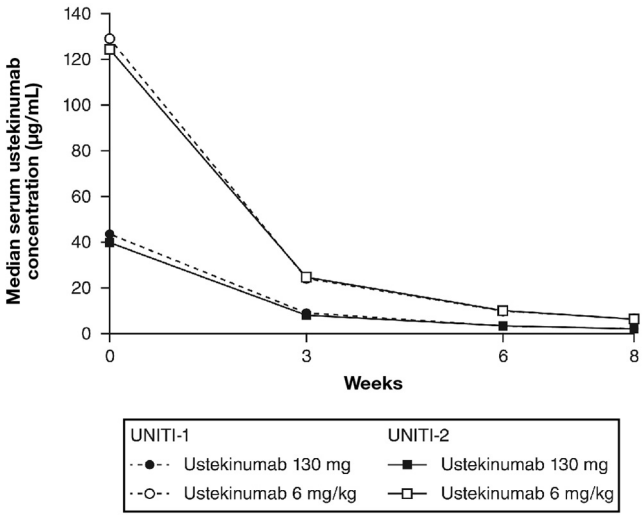


Figure 1. Median serum ustekinumab concentrations illustrating dose proportionality over time during the induction studies UNITI-1 and UNITI-2.

trend was significant in both UNITI-1 ($P = .039$) and UNITI-2 ($P = .007$). Of note, when examining ER within the approved ~6 mg/kg dose, the remission rate remained largely unchanged in UNITI-2 with only an approximately 1% increase in remission rate from the third to the fourth quartile despite concentration doubling (Supplementary Figure 4*B*). Although the ER across the quartiles was not as clear in the UNITI-1 data, the remission rates were not higher in the third or fourth quartile when compared with the second quartile, which had substantially lower concentrations (Supplementary Figure 4*A*). Taken together, these data do not suggest a higher induction dose would have resulted in higher remission rates at week 8 across the population.

In the maintenance study, greater proportions of patients were in clinical remission at week 24 in the higher ustekinumab concentration quartiles (Figure 3*C*). Clinical remission was seen in 55.3% and 70.8% of patients in the 2 lower quartiles, whereas the 2 higher quartiles saw remission rates of 77.1% and 81.3% ($P = .002$). In the lowest quartile, where the lowest remission rates were observed, a substantial majority of patients were receiving the q12w regimen.

When maintenance ER was examined by dosing regimen (q12w and q8w), the proportion of patients in remission was incrementally higher from the second through the fourth quartile for the q12w treatment quartiles (Figure 3*D*, $P = .084$). By contrast, the top 3 quartiles of the q8w treatment all had comparable remission rates of approximately 80% (Figure 3*E*, $P = .006$). Average steady-state trough concentrations were similarly associated with remission at week 44 (maintenance primary endpoint; Supplementary Figure 5, $P = .003$). With respect to endoscopic endpoints at week 44 of maintenance, greater proportions of patients achieved a reduction in the SES-CD score of 3 points or more with increasing ustekinumab concentration (Figure 4*A*, $P = .038$). Further, greater endoscopic response (Figure 4*B*, $P = .006$) and remission rates (Figure 4*C*, $P = .054$) were observed in the top 3 concentration quartiles compared with the first quartile. In all cases, the lowest serum ustekinumab concentration quartile (≤0.5 µg/mL) had notably lower proportions achieving the endoscopic endpoints.

To assess the relationship between ustekinumab exposure and CRP concentration, the distribution of the CRP concentration was also compared across the ustekinumab concentration quartiles. A trend toward lower CRP concentration with increasing ustekinumab concentration was observed at induction week 8 (Supplementary Figure 6*A* and *B*, $P < .001$). Similar patterns were observed during maintenance with steady-state ustekinumab concentration and CRP at week 24 ($P < .001$, Supplementary Figure 6*C*) and week 44 ($P = .008$; Supplementary Figure 6*D*). In addition, a greater proportion of patients had normalized CRP at higher serum ustekinumab concentration ($P < .001$, Supplementary Figure 7). However, as seen in Table 1, baseline CRP concentrations were significantly higher to begin with in the lower concentration quartiles (and were also much lower to begin with in the higher quartiles; Table 1). Additionally, a positive correlation was observed between CRP concentration at baseline and at end of induction (week 8: correlation coefficient $r = 0.58$, $P < .001$) as well as during maintenance (week 24: $r = 0.63$, $P < .001$; week 44: $r = 0.68$, $P < .001$). To correct for this, CRP ER analyses were limited to patients with baseline CRP between 3 mg/L and 10 mg/L, a range chosen to eliminate outliers but still include enough patients to analyze (as most patients are in this range). Interestingly, no statistically significant trend was observed in this subgroup analysis, suggesting that patients with higher baseline CRP may be driving the association noted in the complete dataset.

Estimation of Optimal Ustekinumab Concentration Targets

To identify a concentration of ustekinumab that distinguishes patients with and without clinical remission, ROC curves were generated for remission endpoints during both the induction and maintenance treatment periods. Using serum ustekinumab concentration at week 8 to correlate with remission at week 8, the ROC analysis identified a cutoff of 3.3 µg/mL with an area under the curve (AUC) of 0.57 ($P = .001$); sensitivity and specificity were 0.63 and 0.52, respectively (Figure 5*A*). With respect to maintenance, ROC analyses performed for the combined q8w and q12w regimens resulted in statistically significant AUCs (95% confidence interval 0.64 [0.56–0.70], $P = .003$ using trough concentration at week 24 vs remission at week 24 [Table 2, Figure 5*B*]; and 95% confidence interval 0.62 [0.54–0.69], $P = .011$ using average trough concentration vs remission at week 44 [Table 2, Figure 5*C*]). Similar results were obtained using trough concentration at week 40 vs remission at week 44 for the q8w regimen only (Table 2). ROC analysis using only the q12w data (data not shown) resulted in AUCs that were not statistically significant; thus, a cutoff could not be determined based on only this subgroup. Overall, steady-state serum ustekinumab trough

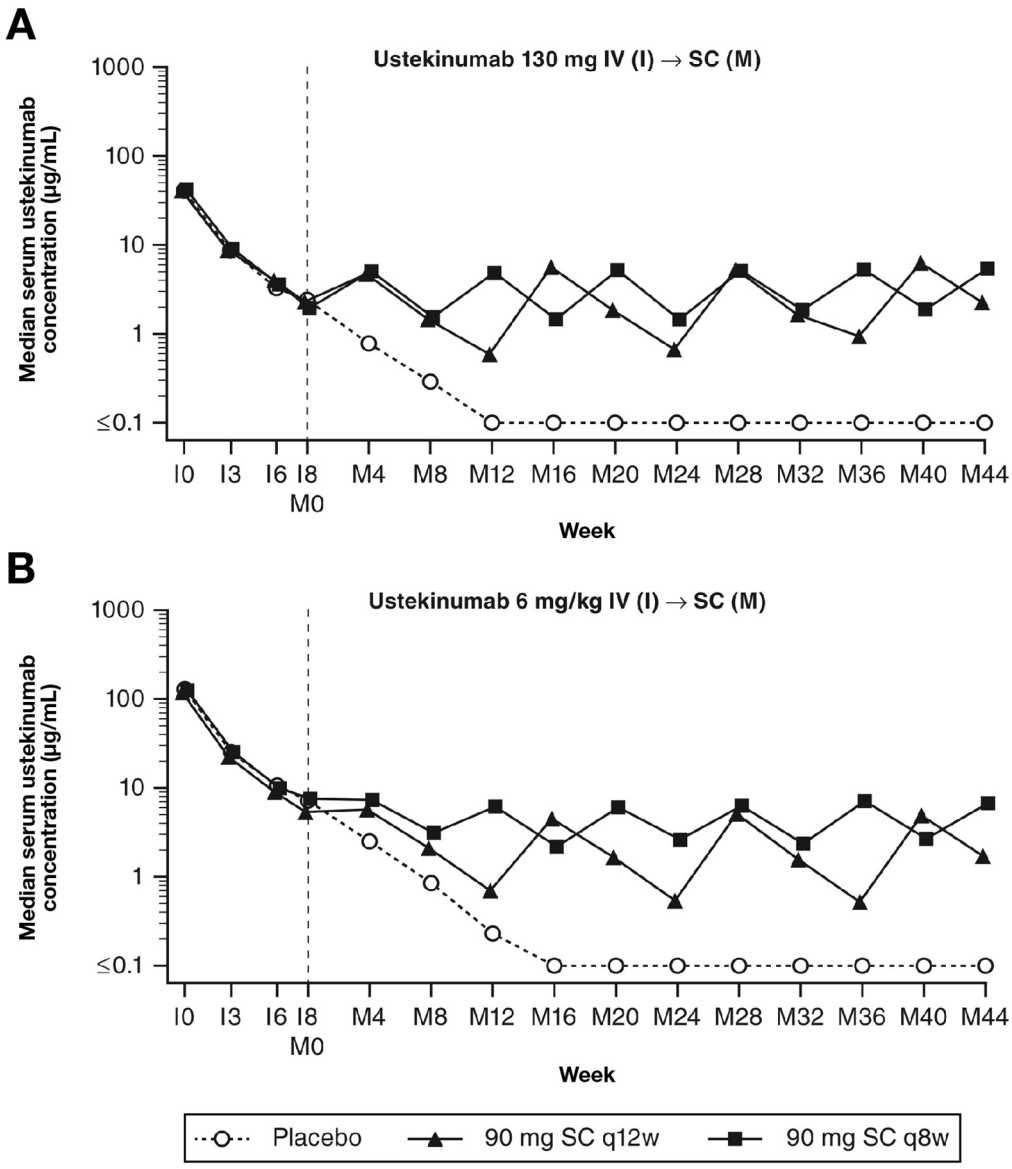


Figure 2. Median serum ustekinumab concentrations over time from induction with a dose of 130 mg (*A*) or ~6mg/kg (*B*) and through the maintenance study IM-UNITI. The patients in the placebo groups in both (*A*) and (*B*) received an IV induction dose of ustekinumab only and were on placebo treatment during maintenance. I, induction; M, maintenance.

concentration targets for clinical remission during maintenance ranged from 0.8 to 1.4 μg/mL.

Immunogenicity

A total of 1154 treated patients who received at least 1 dose of ustekinumab during induction or maintenance had appropriate samples for antibody testing. Of those, 27 patients (2.3%) were positive for antibodies to ustekinumab during at least 1 timepoint through 1 year. Many of these patients were positive at only a single timepoint and then had subsequent negative antibody results. Additionally, 20 of the 27 patients had titers at or below 1:800. Seventeen (63.0%) of the 27 were positive for neutralizing antibodies. Of note, in subjects randomized to maintenance, induction responders who continued to receive ustekinumab maintenance therapy had a lower incidence of anti-ustekinumab antibodies (2.7% [7/263]) compared with the 5.3% (7/133) who did not receive continuous ustekinumab maintenance (ie, induction responders who went on placebo during maintenance). Among treated patients, the proportion positive for antibodies to ustekinumab was 1.9% (7/375) among those who received concomitant immunomodulators and 2.6% (20/779) among patients who did not. Median serum ustekinumab concentrations were generally lower in the few patients who were positive for antibodies. For example, at week 24, median steady-state serum ustekinumab concentration was 0.3 μg/mL in the 5 patients positive for antibodies to ustekinumab compared with 1.1 μg/mL in the 186 patients who were negative. None of the patients who were positive for antibodies to ustekinumab had injection-site, serum-sickness–like, or anaphylaxis reactions.

Safety

Select aggregate adverse events that occurred during these trials have been previously published.[29] No consistent

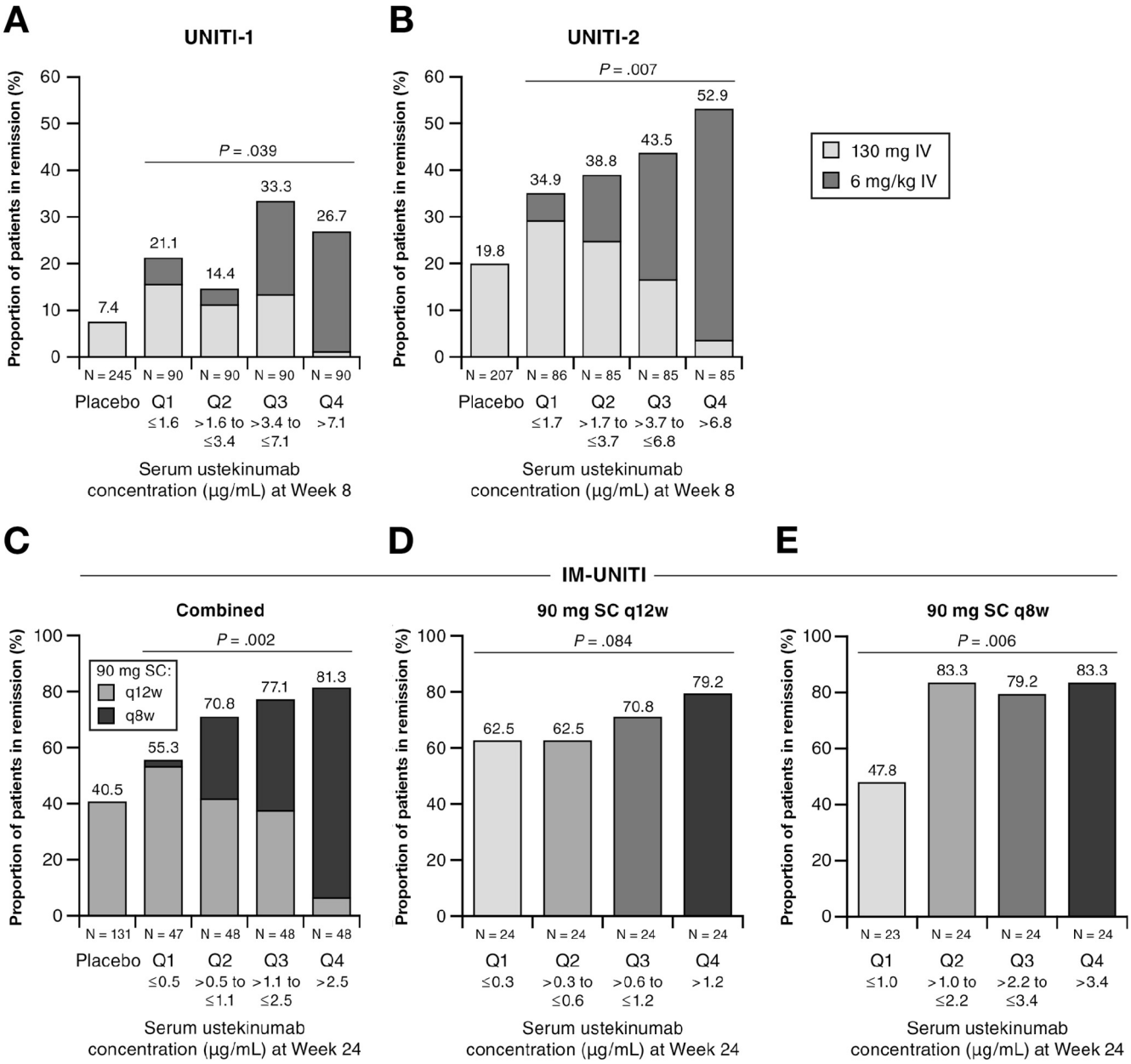


Figure 3. Proportions of patients achieving clinical remission by serum ustekinumab concentration quartiles at week 8 in the UNITI-1 (*A*) and UNITI-2 (*B*) induction studies, at week 24 (*C*) in the IM-UNITI maintenance study, and at week 24 in the q12w (*D*) and q8w (*E*) doses in the IM-UNITI maintenance study. Patients in the placebo group received an IV induction dose of ustekinumab only and were on placebo treatment during maintenance. N, number of patients; Q, quartile.

relationship was observed between ustekinumab concentration and the incidence of infections, serious infections, or serious adverse events during either induction or maintenance (Supplementary Table 3).

Discussion

Ustekinumab, which was approved for CD in the United States, Canada, and European Union in 2016, targets the IL12 and IL23 inflammatory pathways and has a well-established safety profile in clinical trials and clinical practice since its first approval for moderate to severe plaque psoriasis in 2009.[31–33] In the present analyses of the UNITI-1 and UNITI-2 CD induction studies and the IM-UNITI maintenance study, we evaluated the PK of ustekinumab in patients with moderately to severely active CD and provide the first detailed assessments of associations between ustekinumab concentration and efficacy outcomes. This is the most comprehensive PK and ER evaluation of ustekinumab in patients with CD to date. Understanding ustekinumab PK characteristics and the relationship between efficacy outcomes and ustekinumab concentrations is important for prescribers to optimize efficacy with ustekinumab therapy.

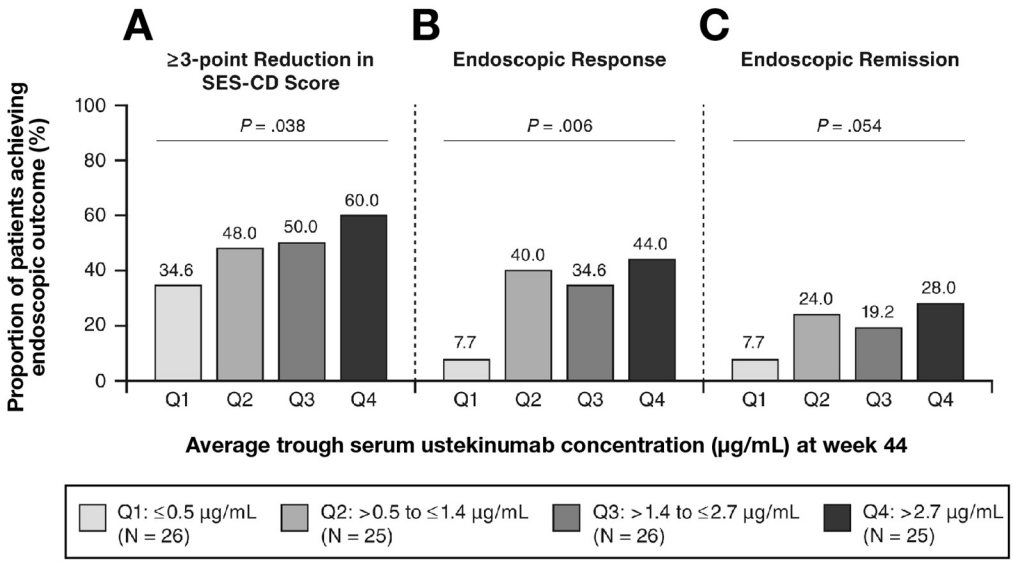


Figure 4. Proportions of patients achieving endoscopic endpoints by serum ustekinumab concentration quartiles at week 44 in the IM-UNITI maintenance study. Reduction in the SES-CD score of ≥3 points (*A*), endoscopic response (*B*), and endoscopic remission (*C*). Average trough concentrations were obtained by computing the arithmetic mean of the observed trough concentration for each patient (q12w: week 24, week 36; q8w: week 24, week 32, and week 40) to reflect average exposure at steady state. N, number of patients; Q, quartile.

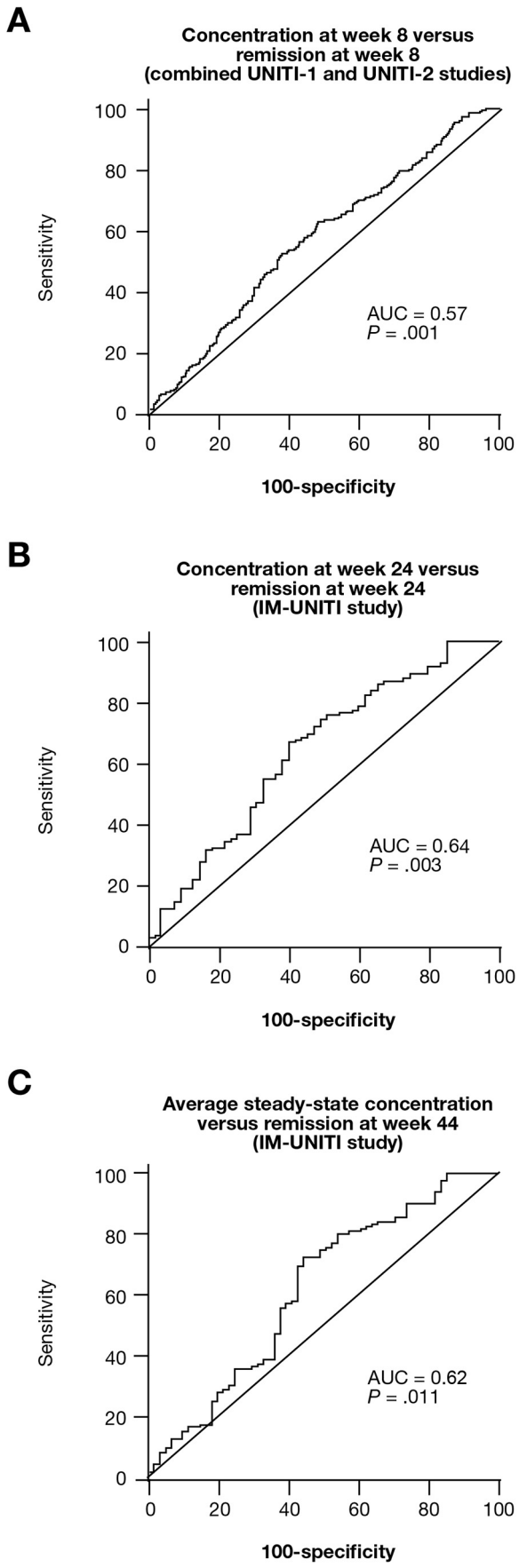
These analyses demonstrated that ustekinumab exhibits dose-proportional PK behavior with IV induction doses of 130 mg and ~6 mg/kg that was similar in patients who did not respond to, lost response to, or were intolerant to treatment with TNF antagonists (UNITI-1 population), as well as in patients who did not respond or were intolerant to conventional therapy and who were predominantly naïve to TNF antagonists (UNITI-2 population). These findings suggest that the clearance of ustekinumab does not vary with dose or study patient population. Therefore, the better efficacy seen in TNF-antagonist–naïve patients compared with TNF-antagonist–failure patients does not seem to be attributable to differences in ustekinumab exposure. The observed dose-proportional profile of ustekinumab allows for the prediction of the impact of dose changes on systemic exposure.

Strong positive associations were seen between ustekinumab concentration and clinical efficacy outcomes in induction. With the approved ~6 mg/kg dose, remission rates appear to have peaked in the higher concentration quartiles. However, in both induction studies, patients in the lowest quartile demonstrated notably lower rates of remission at week 8, suggesting these patients with high drug clearance and baseline disease activity are a population that would be appropriate to consider further induction dose intensification (eg, in future studies).

Similarly, maintenance ER analysis showed strong positive correlations between steady-state trough ustekinumab concentrations (first attained at the time of the second 90-mg SC dose) and remission with both maintenance regimens (90 mg SC q12w and q8w) individually, as well as when the data from the regimens were combined. Within the q8w regimen, efficacy appears to have peaked from the second concentration quartile, suggesting that an efficacy plateau was reached at the exposures attained by most patients. The patients in the lowest quartile ($\leq$0.9 μg/mL) with this regimen achieved a substantially lower clinical remission rate. Data within the 90 mg q12w group was consistent with this observation, as the highest remission rates occurred within the last quartile ($>$1.2 μg/mL) in the q12w group and was comparable with remission rates in patients who fell within or above the second quartile ($>$0.9 μg/mL) in the q8w group. Endoscopic outcomes at week 44 were also notably greater in the 3 higher quartiles ($>$0.5 μg/mL) than in the first quartile ($\leq$0.5 μg/mL).

Based on the ROC analyses, steady-state concentration cutoffs ranging between 0.8 and 1.4 μg/mL were associated with greater clinical remission during maintenance, corroborating the quartile analysis. The range of these target concentrations illustrate that there is some heterogeneity in applying precise level "targets" to individual patients, even when they are valid across a population. In terms of implications for clinical practice, this appears to support shortening the interval to q8w in q12w patients who are not in remission and have trough levels below this range (in regions in which q12w is an approved regimen). Patients on 90 mg q8w in this same circumstance would be a potential population in which to evaluate further dose intensification. Ideally, a future prospective study would examine if better clinical outcomes are achieved by interval shortening (eg, to 6 or 4 weeks) to attain higher trough concentrations above the 0.8 to 1.4 μg/mL target.

In contrast with the previously described findings about ustekinumab concentration thresholds for optimal efficacy, Battat et al[34] recently reported that trough levels above 4.5 μg/mL were associated with biomarker reduction and endoscopic response in a TNF antagonist-refractory



population. Importantly, the study that identified this relatively high trough level was limited by a small sample size (n = 62), the use of SC administration for induction, and the fact that most patients (approximately 75%) received ustekinumab 90 mg every 4 weeks as opposed to the approved q8w or q12w regimens. This is relevant because levels are invariably higher at 4 weeks, specifically, more than twofold higher than at 8 weeks, given ustekinumab's approximately 3-week half-life. In addition, potential differences in the assays used to measure ustekinumab may have contributed to the apparent discrepancy in the proposed concentration threshold. Of the factors evaluated, body weight, serum albumin, and disease severity indicators (CDAI, fecal markers, CRP) were associated with differences in ustekinumab concentration. These findings are consistent with reports of the PK characteristics of some other monoclonal antibodies used in the treatment of IBD.[35,36]

The incidence of antibodies to ustekinumab through 1 year on treatment was 2.3% (using a drug-tolerant assay), indicating that ustekinumab has low immunogenicity. In contrast, the rates of antidrug antibodies with similarly drug-tolerant assays with TNF antagonists are substantially higher with rates of 39.8% for adalimumab[37] and 51% for infliximab[38] in recent reports using drug-tolerant assays. Although lower serum concentrations were observed among those who had antibodies to ustekinumab, there was no demonstrable effect of immunogenicity on efficacy; however, with such a low proportion of patients exhibiting antidrug antibodies, such associations cannot be fully assessed. Importantly, the incidence of antidrug antibodies was slightly higher among those who were randomized to placebo maintenance (5.7%), suggesting that intermittent therapy is a risk factor for immunogenicity, as has been seen with other biologics.[39]

In contrast to the experience with TNF antagonists,[7,40] there was no significant impact of AZA, 6-MP, or MTX on serum ustekinumab concentration and immunogenicity. For TNF antagonists, such as infliximab, the effects of these drugs on PK is hypothesized to be the result of decreased immunogenicity (ie, less tendency to develop anti-drug antibodies), a possible shared mechanism of apoptosis,[7] or a decreased expression of receptors important for monoclonal antibody disposition (for example, Fcγ receptors on monocytes thereby affecting a monoclonal antibody's PK).[41–43] In the case of ustekinumab treatment in patients with CD, the low incidence of anti-ustekinumab antibodies may explain the lack of impact of AZA, 6-MP, or MTX on ustekinumab levels, supporting immunogenicity as the primary driver of

Figure 5. ROC curve analysis of optimal serum ustekinumab thresholds associated with clinical remission at week 8 (*A*) of the combined UNITI-1 and UNITI-2 induction studies, and at week 24 (*B*) and week 44 (*C*) of the IM-UNITI maintenance study. Average trough concentrations were obtained by computing the arithmetic mean of the observed trough concentration for each patient (q12w: week 24, week 36; q8w: week 24, week 32, and week 40) to reflect average exposure at steady state.

Table 2. ROC Analysis Metrics for the Relationship Between Ustekinumab Concentration and Efficacy During the IM-UNITI Study

PK measure	Efficacy endpoint	ROC metric	Value
Trough ustekinumab concentration at week 24 (combined q8w and q12w)	Remission at week 24	AUC (95% CI; *P* value)	0.64 (0.56–0.70; $P = .003$)
		Sensitivity, %	67
		Specificity, %	60
		Threshold, *μg/mL*	0.82
Average trough ustekinumab concentration[a] (combined q8w and q12w)	Remission at week 44	AUC (95% CI; *P* value)	0.62 (0.54–0.69; $P = .011$)
		Sensitivity, %	73
		Specificity, %	56
		Threshold, *μg/mL*	0.80
Trough ustekinumab concentration at week 40 (q8w only)	Remission at week 44	AUC (95% CI; *P*-value)	0.66 (0.54–0.76; $P = .047$)
		Sensitivity, %	82
		Specificity, %	47
		Threshold, *μg/mL*	1.35

CI, confidence interval.
[a]Average of trough ustekinumab concentrations at weeks 24, 32, and 40 for q8w and at weeks 24 and 36 for q12w.

the impact of such drugs on antibody concentration. In contrast to other biologics, because of the apparent lack of need for an immunomodulator, it would seem appropriate to use ustekinumab as monotherapy in CD rather than combination therapy.

In addition to the association of systemic ustekinumab exposure and clinical efficacy variables, we found that ustekinumab concentration was inversely related to CRP concentration and positively correlated with normalization of CRP during both induction and maintenance. Although this points to the possibility that CRP concentration could provide some indication of the effect of treatment, it is difficult to interpret due to the observation that posttreatment CRP is highly correlated with pretreatment CRP. This implies that drug clearance (and therefore ustekinumab concentration) is associated with baseline CRP. This is presumably a function of the higher underlying disease activity, for which CRP is a marker, rather than the CRP molecule itself. Thus, pretreatment CRP may be a potential predictor of ustekinumab concentration in patients receiving ustekinumab.

Regarding safety, we did not observe an association between ustekinumab concentration and infections, serious infections, or serious adverse events. This finding suggests that the occurrence of these safety events is not attributable to the levels of ustekinumab exposure attained with the dose regimens evaluated in these Phase 3 studies.

It is important to acknowledge that these analyses had some limitations. First, the number of patients in the maintenance study decreased over time, which may have implications for the maintenance ER analysis. However, ER analysis using model-predicted ustekinumab concentration data yielded similar results. Second, the ustekinumab concentration cutoffs obtained from the ROC analyses were based on statistically significant but modest AUC and specificity values, which suggest that factors other than serum ustekinumab concentrations (such as markers of inflammatory burden) may need to be evaluated to improve the ability to predict efficacy. In addition, the relatively low specificity associated with the identified thresholds implies that the likelihood of false-positive results (ie, low concentrations occurring in responders) may be high and that additional clinical judgment should be used if patients appear to maintain efficacy despite low concentrations. On the other hand, the relatively higher sensitivity values associated with these thresholds assure treating physicians that levels above these targets are likely adequate to achieve, or maintain, efficacy. Nevertheless, the predictive ability of drug concentration vs efficacy is consistent with those observed from the ROC analyses of TNF antagonists in IBD.[44–46] Finally, although the incidence of antibodies to ustekinumab was low and no impact was observed on efficacy and safety, these results should be interpreted with caution due to the limited number of patients with anti-ustekinumab antibodies in these analyses.

In conclusion, a positive association between ustekinumab concentrations and efficacy outcomes in patients with CD was confirmed during both induction (UNITI-1 and -2) and maintenance (IM-UNITI) studies. The ER findings support the use of both the approved weight-based induction regimen (~6 mg/kg) and the q8w maintenance regimen for the treatment of CD, although a number of patients on the q12w maintenance regimen also attained the ustekinumab concentration cutoff associated with efficacy outcomes. Importantly, ustekinumab concentrations were not influenced by immunomodulators, in marked contrast to infliximab,[7] suggesting ustekinumab can be used as monotherapy and there may be no benefit or need for combination therapy. Although additional studies will be required to determine whether proactive therapeutic drug monitoring to target levels improves long-term CD outcomes, these results from the largest cohort of patients with CD treated with ustekinumab to date (1369 total patients and approximately 100 on each maintenance regimen) can provide important guidance for treating moderately to severely active CD with ustekinumab.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at https://doi.org/10.1053/j.gastro.2018.01.043.

References

1. Baumgart DC, Sandborn WJ. Crohn's disease. Lancet 2012;380:1590–1605.
2. Botoman VA, Bonner GF, Botoman DA. Management of inflammatory bowel disease. Am Fam Physician 1998; 57:57–68; 71–72.
3. Hanauer SB, Meyers S. Management of Crohn's disease in adults. Am J Gastroenterol 1997;92:559–566.
4. Sandborn WJ, Fazio VW, Feagan BG, et al. AGA technical review on perianal Crohn's disease. Gastroenterology 2003;125:1508–1530.
5. Steinberg DM, Cooke WT, Alexander-Williams J. Abscess and fistulae in Crohn's disease. Gut 1973; 14:865–869.
6. Colombel JF, Sandborn WJ, Rutgeerts P, et al. Adalimumab for maintenance of clinical response and remission in patients with Crohn's disease: the CHARM trial. Gastroenterology 2007;132:52–65.
7. Colombel JF, Sandborn WJ, Reinisch W, et al. Infliximab, azathioprine, or combination therapy for Crohn's disease. N Engl J Med 2010;362:1383–1395.
8. Hanauer SB, Sandborn WJ, Rutgeerts P, et al. Human anti-tumor necrosis factor monoclonal antibody (adalimumab) in Crohn's disease: the CLASSIC-I trial. Gastroenterology 2006;130:323–333; quiz 591.
9. Sandborn WJ. The future of inflammatory bowel disease therapy: where do we go from here? Dig Dis 2012; 30(Suppl 3):140–144.
10. Sandborn WJ, Feagan BG, Stoinov S, et al. Certolizumab pegol for the treatment of Crohn's disease. N Engl J Med 2007;357:228–238.
11. Sands BE, Anderson FH, Bernstein CN, et al. Infliximab maintenance therapy for fistulizing Crohn's disease. N Engl J Med 2004;350:876–885.
12. Hanauer SB, Sandborn W, the Practice Parameters Committee of the American College of Gastroenterology. Management of Crohn's disease in adults. Am J Gastroenterol 2001;96:635–643.
13. Travis SP, Stange EF, Lemann M, et al. European evidence based consensus on the diagnosis and management of Crohn's disease: current management. Gut 2006;55(Suppl 1):i16–i35.
14. Hanauer SB, Feagan BG, Lichtenstein GR, et al. Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial. Lancet 2002;359:1541–1549.
15. Rutgeerts P, Feagan BG, Lichtenstein GR, et al. Comparison of scheduled and episodic treatment strategies of infliximab in Crohn's disease. Gastroenterology 2004; 126:402–413.
16. Sandborn WJ, Rutgeerts P, Enns R, et al. Adalimumab induction therapy for Crohn disease previously treated with infliximab: a randomized trial. Ann Intern Med 2007; 146:829–838.
17. Yanai H, Hanauer SB. Assessing response and loss of response to biological therapies in IBD. Am J Gastroenterol 2011;106:685–698.
18. Schreiber S, Khaliq-Kareemi M, Lawrance IC, et al. Maintenance therapy with certolizumab pegol for Crohn's disease. N Engl J Med 2007;357:239–250.
19. Duerr RH, Taylor KD, Brant SR, et al. A genome-wide association study identifies IL23R as an inflammatory bowel disease gene. Science 2006; 314:1461–1463.
20. Neurath MF. IL-23: a master regulator in Crohn disease. Nat Med 2007;13:26–28.
21. Iwakura Y, Ishigame H. The IL-23/IL-17 axis in inflammation. J Clin Invest 2006;116:1218–1222.
22. Kastelein RA, Hunter CA, Cua DJ. Discovery and biology of IL-23 and IL-27: related but functionally distinct regulators of inflammation. Annu Rev Immunol 2007; 25:221–242.
23. Strober W, Zhang F, Kitani A, et al. Proinflammatory cytokines underlying the inflammation of Crohn's disease. Curr Opin Gastroenterol 2010; 26:310–317.
24. Berrebi D, Besnard M, Fromont-Hankard G, et al. Interleukin-12 expression is focally enhanced in the gastric mucosa of pediatric patients with Crohn's disease. Am J Pathol 1998;152:667–672.
25. Monteleone G, Biancone L, Marasco R, et al. Interleukin 12 is expressed and actively released by Crohn's disease intestinal lamina propria mononuclear cells. Gastroenterology 1997;112:1169–1178.
26. Parrello T, Monteleone G, Cucchiara S, et al. Up-regulation of the IL-12 receptor beta 2 chain in Crohn's disease. J Immunol 2000;165:7234–7239.
27. Sandborn WJ, Feagan BG, Fedorak RN, et al. A randomized trial of Ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with moderate-to-severe Crohn's disease. Gastroenterology 2008; 135:1130–1141.
28. Sandborn WJ, Gasink C, Gao LL, et al. Ustekinumab induction and maintenance therapy in refractory Crohn's disease. N Engl J Med 2012; 367:1519–1528.
29. Feagan BG, Sandborn WJ, Gasink C, et al. Ustekinumab as induction and maintenance therapy for Crohn's disease. N Engl J Med 2016; 375:1946–1960.
30. Daperno M, D'Haens G, Van Assche G, et al. Development and validation of a new, simplified endoscopic activity score for Crohn's disease: the SES-CD. Gastrointest Endosc 2004;60:505–512.
31. Leonardi CL, Kimball AB, Papp KA, et al. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 76-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 1). Lancet 2008; 371:1665–1674.
32. Papp KA, Griffiths CE, Gordon K, et al. Long-term safety of ustekinumab in patients with moderate-to-severe psoriasis: final results from 5 years of follow-up. Br J Dermatol 2013;168:844–854.

33. Papp K, Gottlieb AB, Naldi L, et al. Safety surveillance for ustekinumab and other psoriasis treatments from the Psoriasis Longitudinal Assessment and Registry (PSOLAR). J Drugs Dermatol 2015;14:706–714.
34. **Battat R, Kopylov U,** Bessissow T, et al. Association between ustekinumab trough concentrations and clinical, biomarker, and endoscopic outcomes in patients with Crohn's disease. Clin Gastroenterol Hepatol 2017;15:1427–1434.
35. Adedokun OJ, Sandborn WJ, Feagan BG, et al. Association between serum concentration of infliximab and efficacy in adult patients with ulcerative colitis. Gastroenterology 2014;147:1296–1307.e5.
36. Adedokun OJ, Xu Z, Marano CW, et al. Pharmacokinetics and exposure-response relationship of golimumab in patients with moderately-to-severely active ulcerative colitis: results from phase 2/3 PURSUIT induction and maintenance studies. J Crohns Colitis 2017;11:35–46.
37. HUMIRA® [package insert]. North Chicago, IL: AbbVie Inc., 2016.
38. REMICADE® [package insert]. Horsham, PA: Janssen Biotech, Inc., 2015.
39. Hanauer SB, Wagner CL, Bala M, et al. Incidence and importance of antibody responses to infliximab after maintenance or episodic treatment in Crohn's disease. Clin Gastroenterol Hepatol 2004;2:542–553.
40. Colombel JF, Jharap B, Sandborn WJ, et al. Effects of concomitant immunomodulators on the pharmacokinetics, efficacy and safety of adalimumab in patients with Crohn's disease or ulcerative colitis who had failed conventional therapy. Aliment Pharmacol Ther 2017;45:50–62.
41. Witte T. Methotrexate as combination partner of TNF inhibitors and tocilizumab. What is reasonable from an immunological viewpoint? Clin Rheumatol 2015; 34:629–634.
42. Zhou H, Sharma A. Therapeutic protein-drug interactions: plausible mechanisms and assessment strategies. Expert Opin Drug Metab Toxicol 2016:1–9.
43. Wijngaarden S, van Roon JA, van de Winkel JG, et al. Down-regulation of activating Fcgamma receptors on monocytes of patients with rheumatoid arthritis upon methotrexate treatment. Rheumatology (Oxford) 2005; 44:729–734.
44. Cornillie F, Hanauer SB, Diamond RH, et al. Post-induction serum infliximab trough level and decrease of C-reactive protein level are associated with durable sustained response to infliximab: a retrospective analysis of the ACCENT I trial. Gut 2014;63:1721–1727.
45. Reinisch W, Colombel JF, Sandborn WJ, et al. Factors associated with short- and long-term outcomes of therapy for Crohn's disease. Clin Gastroenterol Hepatol 2015;13:539–547.e2.
46. **Mazor Y, Almog R**, Kopylov U, et al. Adalimumab drug and antibody levels as predictors of clinical and laboratory response in patients with Crohn's disease. Aliment Pharmacol Ther 2014;40:620–628.

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Conflicts of interest
Omoniyi J. Adedokun, Zhenhua Xu, Douglas Jacobstein, Philippe Szapary, Jewel Johanns, and Hugh M. Davis are employees of Janssen Research & Development, LLC. Christopher Gasink and Long-Long Gao are employees of Janssen Scientific Affairs, LLC.

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